

The Office Action states that Information Disclosure Statement filed March 26, 1997 fails to comply with the provisions of M.P.E.P. § 609 because an improper form PTO-1449 or equivalent was submitted. Specifically, the Action states that each of the EMBL database submissions listed on the IDS fails to recite the name of the author and the date of publication. The Action also notes that the names of the authors and the dates of publication for these EMBL database submissions have been added to the form PTO-1449, with the corrected document being made of record.

Applicants presume that the Information Disclosure Statement of which the Action refers is the Information Disclosure Statement filed June 20, 2001. Applicants thank the Examiner for correcting the form PTO-1449 by adding the authors' names and publication dates for the EMBL database submissions listed on the IDS. Applicants believe that the corrected form PTO-1449 complies with the provisions of M.P.E.P. § 609, and note that the Action states that the corrected PTO-1449 has been made of record. However, Applicants would be happy to supply an updated copy of the Information Disclosure Statement, and would prefer to have the opportunity if the deficiencies in their previously-submitted Information Disclosure Statement will have the effect of leaving any of the cited references off the front page of any issued patent.

### **3. Objection to the specification**

The Office Action contains an objection to the specification because there are blank spaces in place of an ATCC deposit number on pages 3-5, 9, and 97. Applicants have amended the specification to delete reference to an ATCC deposit number in the specification, and therefore, respectfully request that the objection be withdrawn.

### **4. Rejections of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 101**

The Office Action asserts a rejection of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 101. The Action states that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Applicants traverse this rejection.

Applicants contend that the instant application contains an assertion of a specific and substantial utility for the claimed invention that would be credible to one of ordinary skill in the art.

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[Signature]

Accession No. AAH13644 (replication initiation region protein), which shares the lowest degree of sequence identity with IL-1ra-L polypeptide, *all* of the related amino acid sequences identified in a BLAST search using the IL-1ra-L amino acid sequence (SEQ ID NO: 2) are members of the IL-1 family of proteins (Exhibit A; sequences that were publicly available at the time the instant application was filed are indicated in bold). Based on the knowledge in the art at the time the instant application was filed, Applicants contend that one of ordinary skill in the art would recognize that IL-1ra-L polypeptide is a member of the IL-1 family of proteins. Moreover, as members of the IL-1 family have substantial real world use, for example, as agonists or antagonists of inflammatory responses via binding to an interleukin receptor (Gabay, 2000, *Expert Opin. Investig. Drugs* 9:113-27), Applicants contend that one of ordinary skill in the art would recognize that the claimed molecules have credible, specific, and substantial utility.

Applicants contend that because the instant application contains an assertion of a specific and substantial utility for the claimed invention credible to one of ordinary skill in the art, the rejection under 35 U.S.C. § 101 should be withdrawn.

**5. Rejections of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 112, first paragraph**

The Office Action asserts a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention. The Action states that since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants have set forth affirmative evidence that the asserted utility would be credible to one of ordinary skill in the art. Applicants contend that because the instant application contains an assertion of a specific and substantial utility for the claimed invention that one of ordinary skill in the art would find to be credible, this rejection should be withdrawn.

The Office Action also asserts a rejection of claims 1, 2, 4-8, 10, 11, and 42-46, under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification



a nucleotide sequence complementary to the nucleotide sequence of any of the above nucleic acid molecules. Applicants contend that because claim 2, as amended, recites only fragments of the disclosed human IL-1ra-L nucleic acid molecule (*i.e.*, SEQ ID NO: 1), one of ordinary skill in the art could readily determine the structure of nucleic acid molecules falling within the scope of this claim. Applicants therefore respectfully request that this ground of rejection be withdrawn.

Applicants have amended claim 3 to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution, wherein the encoded polypeptide is at least 70 percent identical to the polypeptide set forth in SEQ ID NO: 2; a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 having a C- and/or N- terminal truncation, wherein the encoded polypeptide comprises at least 25 amino acid residues; a region of the nucleotide sequence of any of these nucleic acid molecules comprising a fragment of at least 16 nucleotides; a nucleotide sequence that hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence of any of the above nucleic acid molecules; or a nucleotide sequence complementary to any of the above nucleic acid molecules. Applicants note that the instant application teaches the amino acid sequence for human IL-1ra-L polypeptide (Figures 1A-1B). The instant application further sets forth in Table I (pages 21-22) rubrics recognized in the art for making conservative amino acid substitutions. In view of the teachings in the instant application, Applicants respectfully contend that one of ordinary skill in the art would understand the scope of species comprising the disclosed genus, and that the inventors were in possession of the invention having said scope at the time the application was filed. Thus, Applicants respectfully contend that their specification fulfills the requirements of 35 U.S.C. § 112, first paragraph, and request that this ground of rejection be withdrawn.

The Office Action also asserts a rejection of claims 2-8, 10, 11, and 42-46, under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for a nucleic acid encoding a polypeptide as set forth in SEQ ID NO: 2, does not reasonably provide enablement for a nucleic acid encoding a polypeptide which is "at least about 70% identical to the polypeptide of SEQ ID NO: 2" or a nucleic acid molecule encoding a substitution, insertion, or deletion mutant of the polypeptide of SEQ ID NO: 2. The Action states that because the claims are overly broad, no guidance is provided

in the art that even a single amino acid change in the amino acid sequence of a protein can have a dramatic effect on that protein's function, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

As described above, Applicants have amended claims 2 and 3 so that they no longer recite nucleic acid molecules comprising either a nucleotide sequence encoding a polypeptide which is at least about 70 percent identical to the polypeptide as set forth in any of SEQ ID NO: 2; a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in any of SEQ ID NO: 1; a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one amino acid insertion; or a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one amino acid deletion. Applicants contend that the claims, as amended, are not overly broad, and that in view of the specification's teachings, one of ordinary skill in the art could readily make and use the claimed nucleic acid molecules. Moreover, Applicants contend that while the references cited in the Action may teach that an amino acid change in the amino acid sequence of a protein can have a dramatic effect on that protein's function, these references do *not* teach that a *conservative* amino acid substitution would have this effect. Specifically, Mikayama *et al.*, 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:10056-60, teach that an asparagine-to-serine substitution at position 106 in human GIF destroys GIF function, and Voet *et al.*, *Biochemistry* 126-28, 228-34 (1990), teach that a glutamic acid-to-valine substitution in beta hemoglobin results in sickle-cell anemia. These are *not* "conservative substitutions" as that term is understood by those with skill in the art *or* as explicitly defined in the instant specification. Applicants note that the instant specification does not teach that an asparagines-to-serine substitution or a glutamic acid-to-valine substitution is either exemplary or preferred (Table I; pages 22-22). Applicants contend that, in view of the specification's teachings and knowledge in the art, it would not require undue experimentation for one of ordinary skill in the art to make and use the claimed invention, and therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, first paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

**6. Rejections of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 112, second paragraph**

The Office Action asserts a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

The Action first asserts that claims 1-3 are indefinite for reciting the phrase "hybridizes under moderately or highly stringent conditions" because this phrase is relative and conditional. The Action states that some nucleic acids that might hybridize under conditions of moderate stringency would fail to hybridize under conditions of high stringency. Applicants note that the specification defines the meaning of the terms "moderately stringent conditions" (page 18, lines 1-7) and "highly stringent conditions" (page 16, line 26 to page 17, line 2), and provides examples of each. However, in order to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention, Applicants have amended claims 1-3 to recite that the claimed nucleic acid molecules comprise a nucleotide sequence that "hybridizes under at least moderately stringent conditions." Applicants contend that the claims, as amended, are not indefinite, and therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claim 2 is vague for reciting the phrase "about 70% identical" because the term "about" is inherently vague and indefinite. As discussed in section 5 above, Applicants have amended claim 2 so that it no longer recites a nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide which is at least about 70 percent identical to the polypeptide as set forth in any of SEQ ID NO: 2. In addition, Applicants have amended claim 2 to replace the term "at least about 25 amino acid residues" with the term "at least 25 amino acid residues," and claims 2 and 3 to replace the term "at least about 16 nucleotides" with the term "at least 16 nucleotides." Applicants contend that the claims, as amended, are not indefinite, and therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claims 2 and 3 are vague and indefinite for reciting the phrase "has an activity of the polypeptide set forth in...SEQ ID NO: 2" because the activity of the polypeptide encoded by the nucleic acid being claimed is unclear. While Applicants respectfully disagree with the assertion that this phrase is indefinite, in an effort to expedite the present application

It is respectfully requested that the Office withdraw the grounds of rejection set forth in this

must comprise at least 25 amino acid residues. Applicants contend that the claims, as amended, are not indefinite, and therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claim 10 is vague and indefinite for reciting the phrase "other than the promoter DNA for the native IL-1ra-L polypeptide" because it is unclear which promoter DNA is being excluded and which is being included in the claim. Applicants have amended claim 10 to recite that "the nucleic acid molecule comprises promoter DNA other than native IL-1ra-L promoter DNA." Applicants contend that because it is clear which promoter DNA is being excluded and which is being included, claim 10 is not indefinite, and therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claim 46 is indefinite for reciting the term "fragment[s] thereof" because this term encompasses potentially any portion of the heterologous polypeptide including a single amino acid. Applicants have amended claim 46 to recite that the IgG constant domain fragment must be "biologically-active," and therefore, respectfully request that this ground of rejection be withdrawn.

The Action next asserts that claims 45 and 46, which are dependent upon non-elected claims 13, 14, or 15, should be amended to be dependent upon on elected nucleic acid claims, since the nucleic acid is utilized in production of the fusion proteins. Applicants have amended claims 45 and 46 to recite a nucleic acid molecule encoding a fusion polypeptide comprising the nucleic acid molecule of any of claims 1, 2, or 3 fused to DNA encoding a heterologous amino acid sequence. Because claims 45 and 46, as amended, are no longer dependent upon non-elected claims 13, 14, or 15, Applicants request that this ground of rejection be withdrawn.

The Action next asserts that claims 4-8, 11, and 42-44 are vague and indefinite for being dependent upon claims 1 and 2 for their limitations. Applicants contend that the claims, as amended, satisfy the requirements of 35 U.S.C. § 112, second paragraph, and therefore, respectfully contend that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

## 7. Rejections of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 102

The Office Action asserts a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 102(a), as being anticipated by International Publication No. WO 99/37662 (published July 29, 1999), contending that this reference discloses a nucleotide sequence of a cDNA molecule encoding a SPOIL protein, which would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1, or which, in the absence of an upper limit to the number of substitutions, deletions, or insertions, would meet the limitations of claim 3. Applicants traverse this rejection.

Applicants first note that the cDNA molecule disclosed in International Publication No. WO 99/37662 shares a sequence identity of 30.2% with the nucleotide sequence of SEQ ID NO: 1 (Exhibit B). In view of the specification's teaching that nucleic acid molecules capable of hybridizing under moderately stringent conditions will share a sequence identity of approximately 79% (page 18, lines 6-7), it is quite apparent that the cDNA molecule disclosed in WO 99/37662 would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under Applicants' recited stringency conditions. In addition, as described in section 6 above, Applicants have amended claim 3 to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution, wherein the encoded polypeptide *is at least 70 percent identical* to the polypeptide set forth in SEQ ID NO: 2. Applicants contend that claim 3, as amended, does not encompass the cDNA molecule disclosed in WO 99/37662. Applicants contend, therefore, that International Publication No. WO 99/37662 cannot anticipate the claims of the instant application, and respectfully request that this ground of rejection be withdrawn.

The Office Action next asserts a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 102(b), as being anticipated by European Patent Application No. EP 0 855 404 (published July 29, 1998), contending that this reference discloses a nucleotide sequence of a cDNA molecule encoding an H<sub>2</sub>-Ira beta protein, which would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1, or which, in the absence of an upper limit to the number of substitutions, deletions, or insertions, would meet the limitations of claim 3. Applicants traverse this rejection.

Respectfully,  
\_\_\_\_\_  
Attorney-in-Fact



(Exhibit C). As discussed above, in view of the specification's teaching that nucleic acid molecules capable of hybridizing under moderately stringent conditions will share a sequence identity of approximately 79%, it is quite apparent that the cDNA molecule disclosed in EP 0 855 404 would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under Applicants' recited stringency conditions. In addition, as described in section 6 above, Applicants have amended claim 3 to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution, wherein the encoded polypeptide *is at least 70 percent identical* to the polypeptide set forth in SEQ ID NO: 2. Applicants contend that claim 3, as amended, does not encompass the cDNA molecule disclosed in EP 0 855 404. Applicants contend, therefore, that European Patent Application No. EP 0 855 404 cannot anticipate the claims of the instant application, and respectfully request that this ground of rejection be withdrawn.

The Office Action next asserts a rejection of claims 1-8, 10, and 42, under 35 U.S.C. § 102(b), as being anticipated by U.S. Patent No. 5,075,222 (issued December 24, 1991), contending that this reference discloses a nucleotide sequence of a cDNA molecule encoding an IL-1ra protein, which would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1, or which, in the absence of an upper limit to the number of substitutions, deletions, or insertions, would meet the limitations of claim 3. Applicants traverse this rejection.

Applicants first note that the cDNA molecule disclosed in U.S. Patent No. 5,075,222 shares a sequence identity of 36.5% with the nucleotide sequence of SEQ ID NO: 1 (Exhibit D). As discussed above, in view of the specification's teaching that nucleic acid molecules capable of hybridizing under moderately stringent conditions will share a sequence identity of approximately 79%, it is quite apparent that the cDNA molecule disclosed in U.S. 5,075,222 would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under Applicants' recited stringency conditions. In addition, as described in section 6 above, Applicants have amended claim 3 to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution, wherein the encoded polypeptide *is at least 70 percent identical* to the polypeptide set forth in SEQ ID NO: 2. Applicants contend, therefore, that U.S. Patent No. 5,075,222 cannot anticipate the claims of the instant application.

that U.S. Patent No. 5,075,222 cannot anticipate the claims of the instant application, and respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 102 have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

### **CONCLUSIONS**

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

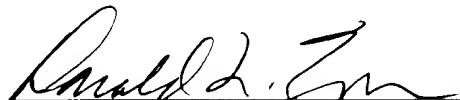
If Examiner Mertz believes it to be helpful, she is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,

**McDonnell Boehnen Hulbert & Berghoff**

Dated: January 16, 2003

By:

  
Donald L. Zuhn, Ph.D.  
Reg. No. 48,710



## EXHIBIT A

BLASTP 2.2.3 [Nov-16-2002]

### Reference:

Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schaffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1990), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", *Nucleic Acids Res.* 25:3389-3402.

PII: 104199813-017484-19574

Query:

1273 letters

Database: All non-redundant GenBank CDS

translations+PDB+SwissProt+PIR+PPF

1,192,592 sequences; 412,925,052 total letters

### Related Structures

### Sequences producing significant alignments:

|   | Score<br>(bits) | E<br>Value |
|---|-----------------|------------|
| gi 1757092 ref NP_055155.1  interleukin 1 family, member 6...   | 290             | 1e-77      |
| gi 1757092 ref NP_062564.1  interleukin 1 family, member 9;...  | 174             | 1e-42      |
| gi 19506601 ref NP_062823.1  interleukin 1 family, member 9;... | 171             | 1e-41      |
| gi 20822740 ref XP_130067.1  IL-1F3 [Mus musculus] >gi 2394...  | 136             | 1e-31      |
| gi 6694394 gb AAF25213.1 AF201833_1 FIL1 eta [Homo sapiens]     | 132             | 7e-30      |
| gi 20822740 ref XP_130067.1  PIKEN cDNA 2310043N20 [Mus mus...  | 114             | 1e-24      |
| gi 25008591 sp Q9D5Z6 ILF8_MOUSE Interleukin 1 family membe...  | 112             | 1e-24      |
| gi 6694392 gb AAF25212.1 AF201832_1 FIL1 zeta [Homo sapiens]    | 70              | 3e-11      |
| gi 19068184 gb AAL671.1.1  IL-1F7d [Homo sapiens]               | 70              | 1e-11      |
| gi 10195738 gb AAG1441.1 AF251119_1 interleukin-1-related ...   | 69              | 1e-11      |
| gi 20127524 ref NP_055254.2  interleukin 1 family, member 7...  | 69              | 7e-11      |
| gi 6912452 ref NP_036407.1  interleukin 1 family, member 5 ...  | 62              | 1e-09      |
| gi 20070152 ref NP_055253.2  interleukin 1 family, member 8...  | 60              | 1e-08      |
| gi 25008591 sp Q9D5Z6 ILF8_MOUSE Interleukin 1 family membe...  | 59              | 7e-08      |
| gi 19506601 ref NP_062823.1  interleukin 1 family, member 5 ... | 59              | 7e-08      |
| gi 23246487 ref NP_094717.1  IL-1F10 [Mus musculus] >gi 250...  | 57              | 1e-07      |
| gi 13624017 ref NP_11444.1  interleukin 1 receptor antagon...   | 57              | 1e-07      |
| gi 238585 gb AAB20265.1  interleukin 1 receptor antagonist ...  | 57              | 4e-07      |
| gi 11559964 ref NP_071530.1  interleukin 1 receptor antagon...  | 57              | 4e-07      |
| gi 1708445 sp P51745 IL1B_CEREL Interleukin-1 beta precurs...   | 57              | 4e-07      |
| gi 198390 gb AAA39310.1  interleukin 1 receptor antagonist      | 57              | 4e-07      |
| gi 1274 emb CAA38566.1  interleukin-1 beta [Ovis aries]         | 56              | 5e-07      |
| gi 124307 sp P21621 IL1B SHEEP INTERLEUKIN-1 BETA PRECURSOR...  | 56              | 6e-07      |
| gi 69700 pir ICB01B interleukin-1 beta precursor - bovine ...   | 56              | 7e-07      |
| gi 6016358 sp P79162 IL1B_CAPHI INTERLEUKIN-1 BETA PRECURSO...  | 55              | 7e-07      |
| gi 3211711 gb AAC39257.1  interleukin-1 receptor antagonist...  | 54              | 2e-06      |
| gi 16166230 sp O18999 IL1X_HORSE INTERLEUKIN-1 RECEPTOR ANTA... | 54              | 2e-06      |
| gi 7438656 pir A39386 interleukin-1 receptor antagonist, 1...   | 54              | 3e-06      |
| gi 2997621 gb AAC39672.1  interleukin-1 intracellular recep...  | 54              | 3e-06      |
| gi 124302 sp P09428 IL1B_BOVIN INTERLEUKIN-1 BETA PRECURSOR...  | 54              | 3e-06      |
| gi 6016361 sp Q29056 IL1X_PIG INTERLEUKIN-1 RECEPTOR ANTAGO...  | 53              | 3e-06      |

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|                                      |   |    |       |
|--------------------------------------|---|----|-------|
| gi 127469 ref NP_115945.3            | putative interleukin-1 recept...          | 51 | 5e-04 |
| gi 127469 gb AAK01472.1              | interleukin-1 receptor antagonis...       | 51 | 8e-04 |
| gi 124314 sp P26890 IL1X_RABIT       | INTERLEUKIN-1 RECEPTOR ANTAG...           | 52 | 1e-05 |
| gi 127469 gb AAK01948.1              | interleukin-1 receptor antagonis...       | 52 | 1e-05 |
| gi 481234 pir  S38373                | interleukin-1 beta precursor - pig >g...  | 50 | 3e-05 |
| gi 127469 gb BAB11808.1              | interleukin-1 receptor antagonis...       | 51 | 3e-05 |
| gi 127469 gb AAL67154.1              | IL-1F7e [Homo sapiens]                    | 49 | 5e-05 |
| gi 6016360 sp O77482 IL1X_BOVIN      | INTERLEUKIN-1 RECEPTOR ANTA...            | 49 | 6e-05 |
| gi 127469 gb AAG14422.1              | interleukin-1-related protein sh...       | 49 | 8e-05 |
| gi 18013002 gb AAL56945.1 AF320322_1 | interleukin-1 precursor...                | 48 | 8e-05 |
| gi 127469 gb AAG38777.1 AF216526_1   | interleukin-1 receptor...                 | 49 | 1e-04 |
| gi 124305 sp P26889 IL1B_PIG         | INTERLEUKIN-1 BETA PRECURSOR (...)        | 48 | 1e-04 |
| gi 6520194 dbj BAA87947.1            | interleukin-1 beta [Tursiops tru...       | 47 | 4e-04 |
| gi 208635 gb AAA72561.1              | interleukin 1-beta                        | 47 | 4e-04 |
| gi 5777787 emb CAB53499.1            | interleukin-1-beta [Xenopus laevis]       | 46 | 4e-04 |
| gi 1708446 sp P51493 IL1B_MACNE      | INTERLEUKIN-1 BETA PRECURSO...            | 46 | 4e-04 |
| gi 1352451 sp P48090 IL1B_MACMU      | INTERLEUKIN-1 BETA PRECURSO...            | 46 | 4e-04 |
| gi 3024024 sp P79182 IL1B_MACFA      | INTERLEUKIN-1 BETA PRECURSO...            | 46 | 4e-04 |
| gi 3687837 gb AAC62237.1             | interleukin-1 receptor antagonist...      | 46 | 5e-04 |
| gi 127469 ref NP_000567.1            | interleukin 1, beta [Homo sapi...         | 46 | 6e-04 |
| gi 127469 gb AAU76442.1              | interleukin-1 beta precursor [Ma...       | 46 | 6e-04 |
| gi 127469 sp P01584 IL1B_HUMAN       | Interleukin-1 beta precursor...           | 46 | 6e-04 |
| gi 424152 pdb 1HIB                   | Interleukin-1 Beta (Human) Mutant With... | 46 | 6e-04 |
| gi 1827779 pdb 1IOB                  | Interleukin-1 Beta From Joint X-Ray A...  | 46 | 7e-04 |
| gi 230410 pdb 21BI                   | Interleukin-1Beta (IL-1Beta) (Mutant W... | 46 | 7e-04 |
| gi 230947 pdb 41BI                   | Interleukin-1Beta (IL-1Beta) (Mutant W... | 46 | 7e-04 |
| gi 230798 pdb 31BI                   | Interleukin-1Beta (IL-1Beta) (Mutant W... | 46 | 7e-04 |
| gi 2905622 gb AAC03536.1             | interleukin 1 beta [Homo sapiens]         | 45 | 7e-04 |
| gi 186288 gb AAA59136.1              | interleukin 1                             | 45 | 7e-04 |
| gi 127469 gb AAK91041.1 AF294754_1   | interleukin-1 beta [Sa...                 | 45 | 9e-04 |
| gi 127469 gb AAU76443.1              | interleukin-1 beta precursor [Pa...       | 45 | 0.001 |
| gi 208637 gb AAA72849.1              | growth hormone:interleukin 1-beta ...     | 45 | 0.001 |
| gi 1170531 sp P41687 IL1B_FELCA      | INTERLEUKIN-1 BETA PRECURSO...            | 45 | 0.001 |
| gi 127469 sp Q28386 IL1B_HORSE       | Interleukin-1 beta precursor...           | 44 | 0.003 |
| gi 7438655 pir  JC5646               | interleukin-1 beta - horse >gi 24635...   | 44 | 0.003 |
| gi 2821975 dbj BAA24538.1            | interleukin-1 beta [Cyprinus car...       | 43 | 0.004 |
| gi 5768097 emb CAB51366.1            | interleukin-1-beta [Cyprinus car...       | 43 | 0.004 |
| gi 1170530 sp P46648 IL1B_CERTO      | INTERLEUKIN-1 BETA PRECURSO...            | 43 | 0.006 |
| gi 3211709 gb AAC39256.1             | interleukin-1 beta [Equus caballus]       | 43 | 0.006 |
| gi 124306 sp P14628 IL1B_RABIT       | INTERLEUKIN-1 BETA PRECURSOR...           | 42 | 0.006 |
| gi 127469 emb CAD11603.1             | interleukin-1 beta [Sparus aura...        | 42 | 0.007 |
| gi 25956174 emb CAC33867.2           | interleukin 1 beta protein [Sco...        | 40 | 0.032 |
| gi 127469 gb AAL18817.1 AF421387_1   | interleukin 1 beta pre...                 | 40 | 0.046 |
| gi 127469 emb CAC83518.1             | interleukin-1 beta [Oncorhynchus...       | 40 | 0.047 |
| gi 3805826 emb CAA06157.1            | interleukin-1 beta [Oncorhynchus...       | 40 | 0.049 |
| gi 127469 dbj BAB86882.1             | IL-1b [Paralichthys olivaceus]            | 39 | 0.061 |
| gi 127469 sp P44701 IL1B_CANF        | Interleukin 1 beta precursor...           | 39 | 0.062 |
| gi 127469 sp P44701 IL1B_TPIVC       | Interleukin 1 beta precursor...           | 39 | 0.062 |
| gi 127469 emb CAC18988.1             | interleukin 1 beta [Cyprinus...           | 39 | 0.11  |
| gi 127469 emb CAC18988.1             | interleukin 1 beta [Cyprinus...           | 39 | 0.11  |
| gi 127469 emb CAC18988.1             | interleukin 1 beta [Cyprinus...           | 39 | 0.11  |
| gi 494810 pdb 2MIB                   | Interleukin-1 Beta (IL-1 Beta) >gi 231... | 35 | 0.77  |
| gi 127469 ref NP_042397.1            | interleukin 1 beta [Mus muscula...        | 34 | 0.84  |
| gi 127469 ref NP_113700.1            | interleukin 1 beta [Rattus nor...         | 34 | 1.1   |
| gi 127469 gb AAH13644.1              | Similar to replication initiatio...       | 34 | 1.4   |
| gi 127469 emb CAF12102.1             | interleukin-1 beta-1 [Parasitus...        | 33 | 3.6   |



**EXHIBIT B**

10 20 30 40 50  
IL-1ra-L ATGAGGCTCAGAAAGATCCATGAGAGAAAGCATGGCTTCCTGGGCTCAGAC  
TATCTCCAGTCTTTCTAGGTACCTCTTTGTACAGAGGAAGCAGTGTG

60 70 80 90 100  
IL-1ra-L ATTCACTGACCACTTCCTTTTGGTGGAGTGAGGGCTCCCTTGGTTATAT  
TAAGTGAGTGTGAGAGGAAGCCGACCTTACCTCGAGGGGAAGCATATA

110 120 130 140 150  
IL-1ra-L GTCACCTCCAGGGTGCGTTGTGCTCCCGCCCTTTTCTTCATTCTCATGAG  
CAGTGAGGTCACCCCAACAACGAGCGGGGGAAAAAGAGTAAGAGGTACC

160 170 180 190 200  
IL-1ra-L GTTGTTTTCCCTGATCAGTCCCAATGCGAGTACCTGGATATATCAGTTGAA  
CAACAAAGGGACTATCTCAGGCTTACCTCATGGACCTATATAGTCAACTT

210 220 230 240 250  
IL-1ra-L GACTTTGAAAGCTTGAGAAAACAGACTATGTTTATGTGAAGCTTTTGTTC  
CTGAAACTTCGGACTCTTTTGTCTGATACAAATACACTTCGAAAACAAAG

260 270 280 290 300  
IL-1ra-L TGGAGATGAAAATAAGAGAGCAAGAGGAATGATGAAAAATTCACTGTT  
ACCTCTACTTTTATGCTCTGCTTTCTCTTACTACTTTTTTAAGTGACAA

310 320 330 340 350  
IL-1ra-L GGACTATATGAAAACTCAGGCTGTGTGTTCATGGTCTTTCAGTGAAGTATT  
CCTGATATACCTTTTGGAGTCAGACAAAGTACAGAAACTCACTTGATAA

360 370 380 390 400  
IL-1ra-L TTCAACATTGAAAAATTGACACACCTCAGCGGAGGAGCATTGAGGATATCA  
AAGTTGTAAATTTTAACTGTGTGGAGTGGCCCTCTGTAAGTCTATAGT

41 42 43 44 45  
IL-1ra-L ATGATGCTGCTGCTGCTTTCTTGGGAGAGAGCTATAGAGAGTCTGAGG  
TATGATGAG

46 47 48 49 50  
IL-1ra-L TATTCA--ATCAG--GCTCA-ATCTGAGGATTGG  
TCTTCTGAG



710            720            730            740            750  
 IL-1ra-L    AGTCTGTGGGCTTTCCCTGGCTGGTTTCATCGCTGTGAGCTCTGAAAGGAGGC  
              TCAGACACCGAAAGGGACCGACCAAGTAGCGACAGTGGAGACTTCCTCG

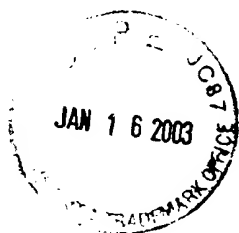
1. SPCIL I    0            320            330            340            350  
 [ 604 ]       AGTCTGTGGGCTTTCCCTGGCTGGTTTCATCGCTGTGAGCTCTGAAAGGAGGC  
              |||||    || |||||    |||||    |||||    |||||    |||||    |||||  
 IL-1ra-L    AGTCTGTGGGCTTTCCCTGGCTGGTTTCATCGCTGTGAGCTCTGAAAGGAGGC

760            770            780            790            800  
 IL-1ra-L    TGTCTCTCTCATCTTACCCAAAGAACTGGBGAAAGCCAACTACTGACTT  
              AACGAGAGATAGGAATGGGTTCTTGACCCCTTTCGGTTGTGATGACTGAA

1. SPCIL I    0            370            380            390            400  
 [ 604 ]       TGTCTCTCTCATCTTACCCAAAGAACTGGBGAAAGCCAACTACTGACTT  
              || || |||||    || |||||    |||||    || || || |||||  
 IL-1ra-L    TGTCTCTCTCATCTTACCCAAAGAACTGGBGAAAGCCAACTACTGACTT

810  
 IL-1ra-L    TGGGTAACTATGCTGTTT  
              ACCCAATTGATACGACAAA

1. SPCIL I    0            420  
 [ 604 ]       CGAGATGATTGTGGT>  
              || || || || || ||  
 IL-1ra-L    TGGGTAACTATGCT



## EXHIBIT C

10 20 30 40 50  
IL-11a-L ATGAGGCTCAAAAAATCCATGGAGAAACATGGCTTCTCTGGGCTCAAC  
TCTATGCAATGTTTCTGCTAGCTCTTTCTATACCAAGGACCAAGATCTG

IL-1 $\alpha$ -L      ATTCACTCAGCACTTCCCTTTGGCTGGGATGGGGGCTCCCTTGGTTACAT  
TAAGTGASTGGGTGAAGGAAACCGATCCTCACCCCGAGGGAACCAATGTA

119 120 130 140 150  
11-119-L GTCA TDCAGGSGTGGGTTGTGTGCTGCCCCCGTTTTCCTTCATTCTCATG  
CAGTGAAGGTCCCAAGCAACGAGAGGGGGGGAAAAGAAGTAAGAGGATACC

|                  |  |     |     |     |     |
|------------------|--|-----|-----|-----|-----|
|                  | 160  | 170 | 180 | 190 | 200 |
| IL-1 $\alpha$ -L | GTGTGTTTCCCTGATCAAGTCCCAATGGGASTAAGTGGATATATCAGTTGAA |     |     |     |     |
|                  | CAACAAAGGGCACTAGTCAGGGTTACGCTCATGGACCTATATATGTCAACTT |     |     |     |     |

|          |                               |                       |                              |                      |     |
|----------|-------------------------------|-----------------------|------------------------------|----------------------|-----|
|          | 210                           | 220                   | 230                          | 240                  | 250 |
| IL-1ra-L | GACTTTTGAAGCCTGAGAAAACAGACTAT | GTTCATGTGAAGCTTTTGTTC | CTGAAACTTGGGACTCTTTTGTCTGATA | CAATAACTTCGAAAACAAAG |     |

1. IL-1ra β  
[ 1002 ]

IL-1ra-L

IL-1ra-L

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1. IL-1ra β C      40      50      60      70
[ 1002 ]  TGTAGAT--AAAGA-CCCTTTCTTGCCA GGTGCT SAGACAA-CCACACTA>
           || |||  ||| ||  |  |  || ||| ||  ||  ||| |
IL-1ra-L  TGGAGATGAAATATGCGAGGCCCAAGAGGAAT TATGAAAAAATTCACTGTT

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11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1041 1042 1043 1044 10

1. 11. 1ra β                  80                  90                  100                  110                  120  
[1. 1. 1] TG---AGAG-GCACTC-CAGGAGA/GGTGAT/GTGAAGAA/TGGGGTTGT>  
          |   |   |      |||   |   |   |   |   |   |  
[1. 1. 6] GGA-TTATTGAAAA-TGGGKTGT-ETTTACTKE-TTTTGCTTAA-TAATT



|                               |  |   |     |     |         |     |     |     |
|-------------------------------|--|---|-----|-----|---------|-----|-----|-----|
|                               |  | 300   | 350 | 400 | 450     | 500 | 550 | 600 |
| IL-1ra-L                      |  | TTCAACATTGAAAATTGACACACCTCAGCGCGGGGACGATTTCAGGATATCA<br>AAATTGTAACTTTTAACTTTSTSTGGAATAGCGAATCTCTAACTATATAGT |     |     |         |     |     |     |
| 1. IL-1ra $\beta$<br>[ 1002 ] |  | 130   | 140 | 150 | 160     | 170 | 180 | 190 |
|                               |  | ATCAA---TCA-ATSTG-TAAACCTATTACTGGGAATATTAATGATTTGAG<br>   |     |     |         |     |     |     |
| IL-1ra-L                      |  | TTCAACATTGAAAATTGACACACCTCAGCGCGGGGACGATTTCAGGATATCA  |     |     |         |     |     |     |
|                               |  | 410   | 420 | 430 | 440     | 450 |     |     |
| IL-1ra-L                      |  | ATCATCGGGTGTGGTTCTTCAGGACGAGAGATCATAGCACTCCGAGGG<br>TAGTAGGCCACACCGAAGAACTCTGGTGTGAGAGTATAGTTCAAGGATCC      |     |     |         |     |     |     |
| 1. IL-1ra $\beta$<br>[ 1002 ] |  | 170   | 180 | 190 | 200     | 210 |     |     |
|                               |  | ATCAGCAAGTGTGAGACCTTCAGGGTCAGAAACCTTGTGGCACTCCAGG<br>   |     |     |         |     |     |     |
| IL-1ra-L                      |  | ATCATCGGGTGTGAGTTCTTCAGGACGAGAGCTCATAGCACTCCGAGGG   |     |     |         |     |     |     |
|                               |  | 460   | 470 | 480 | 490     | 500 |     |     |
| IL-1ra-L                      |  | AAGGACCGTATGTCTCCAGTCACTATTGCGCTTAATCTCATGCGGACATGT<br>TTCCTGGCATAACAGAGGTCACTGATAACGGAATTAGAGTACGGCTGTACA  |     |     |         |     |     |     |
|                               |  | T<br>   |     |     |         |     |     |     |
| 1. IL-1ra $\beta$<br>[ 1002 ] |  | 220   | 230 | 240 | 250     | 260 |     |     |
|                               |  | AAGGACAGTGTGACCCCAAGTCACTGTTGCTGTTATCAGATGCAAGTATCC<br>   |     |     |         |     |     |     |
| IL-1ra-L                      |  | AAGGACCGTATGTCTCCAGTCACTATTGCGCTTAATCTCATGCGGACATGT   |     |     |         |     |     |     |
|                               |  | 510   | 520 | 530 | 540     | 550 |     |     |
| IL-1ra-L                      |  | GGAGACCCCTTGAGAAAGACAGAGGGGACCCCATCTACCTGGGCGCTGAATG<br>CCTCTGGGAACTCTTTCTGTCTCCCTGGGGTAGATGGACCCGGACTTAC   |     |     |         |     |     |     |
|                               |  |   |     |     | AAT<br> |     |     |     |
| 1. IL-1ra $\beta$<br>[ 1002 ] |  | 270   | 280 | 290 | 300     |     |     |     |
|                               |  | AGAGGGCTCTTGAGCAAGGCAGAGGGGATCCCATTTATTTGGGCGAGAATC<br>   |     |     |         |     |     |     |
| IL-1ra-L                      |  | TTAGGACCTTGAAGACCAATAGAGGGAATATCTATCTGTAATCTGATG  |     |     |         |     |     |     |
|                               |  | 310   | 320 | 330 | 340     | 350 |     |     |
| IL-1ra-L                      |  | GACTTAATCTTCACTGATCTCTCTAAAGTCTTCTGCTGCTGCTGCTGCTG<br>CTGAGTTAGAGAGGGAATACACAGGATTCAGACCACTGCTGGGTGTGAG     |     |     |         |     |     |     |
| 1. IL-1ra $\beta$<br>[ 1002 ] |  | 360   | 370 | 380 | 390     | 400 |     |     |
|                               |  | CA-GGAATCTGTTTGTATGTAAGCAAGCTTCAGGAGAGGATTAATG<br>  |     |     |         |     |     |     |
| IL-1ra-L                      |  | CACTAATCTTCACTGATCTCTCTAAAGTCTTCTGCTGCTGCTGCTGCTG   |     |     |         |     |     |     |



## EXHIBIT D





510  
 IL-1ra-L TGGGTAACTATGCTGTTT  
 ACCCAATTGATAGGACAAA

540  
 IL-1ra  
 [ 32 ] AAATTCTACT-TCCAG  
 | | | | |  
 IL-1ra-L TGGGTAACTATGCTG



AMENDMENTS TO THE SPECIFICATION

Marked Up Version of Replacement Paragraphs of Specification

under 37 C.F.R. 1.121(b)(1)(iii)

Please amend the title at page 2, lines 1-2 to read as follows:

NUCLEIC ACIDS ENCODING INTERLEUKIN-1 RECEPTOR ANTAGONIST-LIKE  
MOLECULES, ~~PROTEINS~~ AND USES THEREOF

Please amend the paragraphs at page 3, line 16 to page 4, line 16 to read as follows:

The invention provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

- (a) the nucleotide sequence as set forth in SEQ ID NO: 1;
- ~~(b) the nucleotide sequence of the DNA insert in ATCC Deposit No. \_\_\_\_\_;~~
- ~~(e)~~(b) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2;
- ~~(d)~~(c) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of either (a) - ~~(e)~~ or (b); and
- ~~(e)~~(d) a nucleotide sequence complementary to any of (a) - (c).

The invention also provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

- (a) a nucleotide sequence encoding a polypeptide which is at least about 70 percent identical to the polypeptide as set forth in SEQ ID NO: 2, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2;
- (b) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in SEQ ID NO: 1, ~~the nucleotide sequence of the DNA insert in ATCC Deposit No. \_\_\_\_\_~~, or (a);

(c) a region of the nucleotide sequence of SEQ ID NO: 1, ~~the DNA insert in ATCC Deposit No. \_\_\_\_\_~~, (a), or (b) encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the encoded polypeptide as set forth in SEQ ID NO: 2, or is antigenic;

(d) a region of the nucleotide sequence of SEQ ID NO: 1, ~~the DNA insert in ATCC Deposit No. \_\_\_\_\_~~, or any of (a) - (c) comprising a fragment of at least about 16 nucleotides;

(e) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) - (d); and

(f) a nucleotide sequence complementary to any of (a) - (d).

Please amend the paragraphs at page 5, lines 12-29 to read as follows:

The present invention provides for an isolated polypeptide comprising an amino acid sequence ~~selected from the group consisting of:~~

~~\_\_\_\_\_ (a) \_\_\_\_\_ the amino acid sequence as set forth in SEQ ID NO: 2; and~~

~~\_\_\_\_\_ (b) \_\_\_\_\_ the amino acid sequence encoded by the DNA insert in ATCC Deposit No. \_\_\_\_\_~~

The invention also provides for an isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) an amino acid sequence for an ortholog of SEQ ID NO: 2;

(b) an amino acid sequence which is at least about 70 percent identical to the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2;

(c) a fragment of the amino acid sequence set forth in SEQ ID NO: 2 comprising at least about 25 amino acid residues, wherein the fragment has an activity of the polypeptide set forth in SEQ ID NO: 2, or is antigenic; and

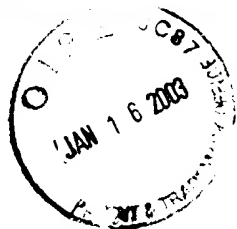
(d) an amino acid sequence for an allelic variant or splice variant of the amino acid



Please amend the paragraph at page 8, line 29 to page 9, line 3 to read as follows:

The terms "IL-1ra-L gene" or "IL-1ra-L nucleic acid molecule" or "IL-1ra-L polynucleotide" refer to a nucleic acid molecule comprising or consisting of a nucleotide sequence as set forth in SEQ ID NO: 1, a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2, ~~a nucleotide sequence of the DNA insert in ATCC Deposit No. \_\_\_\_\_,~~ and nucleic acid molecules as defined herein.

Please delete the paragraph at page 97, lines 26-29.



## AMENDMENTS TO THE CLAIMS

### Marked Up Versions of Amended Claims under 37 C.F.R. 1.121(c)(1)(ii)

1. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

- (a) ~~the nucleotide sequence as set forth in SEQ ID NO: 1;~~
- (b) ~~the nucleotide sequence of the DNA insert in ATCC Deposit No. \_\_\_\_\_;~~
- (e)(b) ~~a nucleotide sequence encoding the~~ a polypeptide as set forth in SEQ ID NO: 2;
- (d)(c) ~~a nucleotide sequence which~~that hybridizes under at least moderately or highly stringent conditions to the complement of any of the nucleotide sequence of either (a) —(e) or (b); and or
- (e)(d) ~~a nucleotide sequence complementary to the nucleotide sequence of~~ any of (a) - (c).

2. (Amended) An isolated nucleic acid molecule comprising ~~a nucleotide sequence~~ selected from the group consisting of:

- (a) ~~a nucleotide sequence encoding a polypeptide which is at least about 70 percent identical to the polypeptide as set forth in SEQ ID NO: 2, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2;~~
- (b) ~~a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in SEQ ID NO: 1, the nucleotide sequence of the DNA insert in ATCC Deposit No. \_\_\_\_\_, or (a);~~
- (c)(a) ~~a region of the nucleotide sequence of SEQ ID NO: 1, the DNA insert in ATCC Deposit No. \_\_\_\_\_, (a), or (b) encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the encoded polypeptide as set forth in SEQ ID NO: 2, or is antigenic;~~
- (d)(b) ~~a region of the nucleotide sequence of SEQ ID NO: 1, the DNA insert in ATCC Deposit No. \_\_\_\_\_, or any of (a) —(c) comprising a fragment of at least about 16~~

(e)(c) a nucleotide sequence ~~which~~ that hybridizes under at least moderately ~~or~~ highly stringent conditions to the complement of ~~any of the nucleotide sequence of either (a) - (d) or (b);~~ and or

(f)(d) a nucleotide sequence complementary to the nucleotide sequence of any of (a) - (d)(c).

3. (Amended) An isolated nucleic acid molecule comprising ~~a nucleotide sequence selected from the group consisting of:~~

(a) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution, wherein the encoded polypeptide ~~has an activity of~~ is at least 70 percent identical to the polypeptide set forth in SEQ ID NO: 2;

(b) ~~a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one amino acid insertion, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2;~~

(c) ~~a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one amino acid deletion, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2;~~

(d)(b) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 ~~which~~ having a C- and/or N- terminal truncation, wherein the encoded polypeptide ~~has an activity of the polypeptide set forth in SEQ ID NO: 2~~ comprises at least 25 amino acid residues;

(e)(c) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one modification ~~selected from the group consisting of that is a conservative amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and/or N-terminal truncation,~~ wherein the encoded polypeptide ~~has an activity of~~ is at least 70 percent identical to the polypeptide set forth in SEQ ID NO: 2 and comprises at least 25 amino acid residues;

(f)(d) a region of the nucleotide sequence of any of (a) - (e)(c) comprising a fragment of at least ~~about~~ 16 nucleotides;

(h)(f) a nucleotide sequence complementary to the nucleotide sequence of any of (a) - (e).

10. (Amended) The process of Claim 8, wherein the nucleic acid molecule comprises promoter DNA other than ~~the promoter DNA for the native IL-1ra-L polypeptide~~ promoter DNA operatively linked to ~~the DNA~~ a nucleic acid molecule encoding ~~the an~~ an IL-1ra-L polypeptide.

11. (Amended) The isolated nucleic acid molecule according to Claim 2, wherein the percent identity is determined using a computer program ~~selected from the group consisting of that is~~ GAP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and or the Smith-Waterman algorithm.

45. (Amended) A nucleic acid molecule encoding a fusion polypeptide comprising ~~the polypeptide~~ nucleic acid molecule of any of Claims ~~13, 14, or 15~~ 1, 2, or 3 fused to DNA encoding a heterologous amino acid sequence.

46. (Amended) ~~The fusion polypeptide~~ nucleic acid molecule of Claim 45, wherein the DNA encoding the heterologous amino acid sequence ~~is encodes~~ encodes an IgG constant domain or biologically active fragment thereof.